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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,348	07/13/2001	Avi Ashkenazi	10466/55	3826

35489 7590 12/24/2008

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/905,348
Filing Date: July 13, 2001
Appellant(s): ASHKENAZI ET AL.

Christopher De Vry
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 29 September 2008 appealing from the Office action mailed 27 December 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal directed to the polypeptide referred to as PRO232. However, there are other applications by the same assignee relying upon the gene amplification assay for utility which are under similar rejections and/or appeals.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in

the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because on page 3 of the brief it states in lines 5-6 that the limitation of amplification in human lung and colon cancers as compared to normal noncancerous human tissue controls is specifically recited in Claims 44(a) and 45 , and carried by all claims dependent from Claim 44. Claim 44(a) and 45 are only directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:18. Claim 44(c) recites that the amino acid sequence of the polypeptide is encoded by the cDNA deposit and wherein "the nucleic acid encoding said polypeptide is amplified in lung or colon tumors". Therefore, the claims do not specifically recite the feature of "being significantly amplified in human lung and colon cancers as compared to normal, non-cancerous human tissue controls".

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Konopka et al. ”Variable Expression of the Translocated c-abl Oncogene in Philadelphia-Chromosome-Positive B-Lymphoid Cell Lines from Chronic Myelogenous Leukemia Patients” Proc. Natl. Acad. Sci. USA, vol83 (1986), pp. 4049-4052.

Pennica et al. "WISP Genes Are Members of the Connective Tissue Growth Factor Family That Are Up-Regulated in WNT-1-Transformed Cells and Aberrantly Expressed in Human Colon Tumors” ” Proc. Natl. Acad. Sci. USA, vol95 (1998), pp. 14717-14722.

Godbout et al. "Overexpression of a DEAD Box Protein (DDX1) in Neuroblastoma and Retinoblastoma Cell Lines” J. Biol. Chem. vol273, no33 (14 August 1998), pp. 21161-21168.

Li et al. “Identification of Putative Oncogenes in Lung Adenocarcinoma by a Comprehensive Functional Genomic Approach” Oncogene, vol25 (2006), pp. 2628-2635.

Sen, S. "Aneuploidy and Cancer" Curr. Opin. Oncol., vo112 (2000), pp. 82-88.

Hittleman, W.N. "Genetic Instability in Epithelium Tissues at Risk for Cancer" Ann. NY Acad. Sci., vol:952 (2001), pp. 1-12.

Rosenthal et al. (DE 19818619-A1, 28 October 1999).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-46 and 49-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 44-46 and 49-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The claims are directed to isolated polypeptides comprising the amino acid sequence of SEQ ID NO:18 with or without its signal peptide, or the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209250, wherein the nucleic acid encoding said polypeptide is amplified in lung and tumor cell carcinomas. It is noted that the phrase “wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors” is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic

acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity. Claims are also presented to chimeric proteins comprising the aforementioned polypeptides. The specification discloses the polypeptide of SEQ ID NO: 18, also known as PRO232. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 24 September 2007), p. 5, beginning of arguments.

At pages 227- 235 of the specification, Example 92 discloses a gene amplification assay in which genomic DNA encoding PRO232 had a ΔCt value of at least 1.0 for five out of nineteen lung tumor samples and seven out of 17 colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 92 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer. ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 230-234 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were

obtained that were at least 2.

While these data are pertinent to utility and enablement of PRO232 *genomic DNA* for use in lung or colon tumor diagnosis, the data do not directly bear on the utility of the claimed PRO232 *polypeptides*. It is noted that the amplification in lung or colon tumors of the nucleic acid encoding the PRO232 polypeptide is not an activity of the polypeptide, but rather a characteristic of a nucleic acid. In order for PRO232 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and, subsequently, increased polypeptide levels. No data regarding PRO232 mRNA or PRO232 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, Pennica et al. (1998, PNAS USA 95:14717-14722, previously of record), disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (p. 14722, second paragraph of left column)

Additional details are provided in the section entitled, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors" on pp. 14720-14721. See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052, previously of record), who state in the abstract that, "Protein expression is not related to amplification of the *abl*

gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph1 template."

Godbout et al. (J. Biol. Chem 273(33):21161, 1998) teaches in the abstract that, "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene had been characterized as being a putative RNA helicase, a type of enzyme that would be expected to confer a selective advantage to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state:

> It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell (48, 49)." For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons.

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO232 gene. It is not disclosed, and based upon the sequence searches in this case the Examiner can not find any reason to suspect, that the protein encoded by the PRO232 gene would confer any selective

advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Therefore, one of skill in the art would *not* expect PRO232 overexpression even if the genomic DNA is amplified. Further, it could not be determined whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO232.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, paragraph beginning at the bottom of col. 1, Li et al. state:

> Although the main focus of this study was to specifically identify putative oncogenes, it should be noted that 90.7% of the genes showing high protein expression did not show corresponding increases in both DNA copy number and transcript, a finding consistent with that of others that transcriptional, translational, and post-translational regulatory mechanisms can greatly influence the abundance of portein in lung tumorigenesis (Chen *et al.*, 2002).... In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

The findings of Li et al. are that over half of the genes which were amplified were not overexpressed at the mRNA level. These findings show one cannot reasonably conclude that genomic amplification correlates with elevated mRNA levels.

While the Examiner has the resources to cite only a handful of references showing the unpredictability of a correlation between genomic DNA and protein levels,

these references stand to show that one cannot make assumptions about the use of PRO290 polypeptide in view of the methods used and information provided in the instant specification. Data pertaining to PRO232 genomic DNA do not indicate anything significant regarding the claimed PRO232 polypeptides. Neither the data nor the art support the specification's assertion that PRO232 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO232 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO232 polypeptide levels are also different between specific cancerous and corresponding normal tissues, the proposed use of the PRO232 *polypeptides* as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are proper.

Claim Rejections - 35 USC § 102

As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. §§ 101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 13 July 2001. Applicant's belief that they are entitled to the filing date of September 17, 1997 is noted, but not persuasive in view of the rejections of record.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44 and 46 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rosenthal et al. (DE 19818619-A1, 28 October 1999) for the reasons of record in the previous Office action(s).

Rosenthal et al. disclose a protein which has an amino acid sequence that is 95-98% identical to that of the claimed protein of SEQ ID NO:18 (SEQ ID NO:82 at page 111 and claim 23). The differences in the amino acid sequence are at the N-terminal portion of the protein, which would be in the "signal sequence" portion of the protein. Therefore, the protein of Rosenthal et al. meets the claim limitations in which the signal sequence is missing.

(10) Response to Argument

ISSUE 1: 101/112, First Paragraph rejections of claims 44-46 and 49-51 based on the results of the gene amplification assay

At pages 4-5 and 10 of Appellants' brief, it is argued that the data in Example 92 (starting at p. 222 of the specification) describes results of a gene amplification assay. Appellants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellants report that the gene encoding PRO232 was significantly amplified (2.056-fold to 5.28-fold) in 5/19 lung tumor samples and 7/17 colon tumor samples. This has been fully considered but is not found to be persuasive. First, it is important to note that the gene encoding PRO232 was found not to be amplified in 14 out of 19 lung tumors and 10/17 colon tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (page 228 of the specification). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy (see, *e.g.,* Sen et al., J. Biol. Chem. 273(33):21161-21168, 1998, and Hittelman et al., Ann N.Y. Acad, Sci 952:1-12, 2001, previously cited). Given these details, one skilled in the art would not conclude that the gene encoding PRO232 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed

polypeptides, since amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA or polypeptide levels (see Pennica et al., Konopka et al., Godbout et al. and Li et al.).

Appellant argues (page 4, page 10, page 13-14, and page 19 through page 21) that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the corresponding mRNA and encoded polypeptide are also expressed at an elevated level. Appellant refers to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Additionally, it is argued that Hyman et al. and Pollack et al. did not use traditional CGH analysis to identify amplified genes, while they did analyzed copy number on a gene-by-gene basis. These arguments have been fully considered but are not found to be persuasive. Orntoft et al. looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region (see for example, page 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with clusters of chromosomal material containing strong gains, but it is not known whether PRO232 is in a gene cluster in a region of a chromosome that is highly amplified, which is pertinent because Orntoft et al. only provide information about genes in clusters (large

chromosomal regions). The data of Orntoft et al. are not from looking at a 1:1 correspondence of genomic DNA and the mRNA which is transcribed from it. If PRO232 is not part of a cluster showing strong gains, then the findings of Orntoft et al. are not applicable. Because no such information was disclosed for PRO232, Orntoft et al. does not support Appellant's position. Ornoft et al. go on to say that detection was very limited.

While Hyman et al. and Pollack et al. combined CGH with microarray analysis, the results do not support a conclusion that the skilled artisan would reasonably expect amplified genomic DNA to correspond with overexpression of encoded protein. Hyman et al. used CGH in combination with cDNA microarray analysis. Less than half (44%) of *highly* amplified genes showed mRNA overexpression, and 10.5% of highly overexpressed transcripts had amplified genes (p. 6242, col. 1, third full paragraph). Thus, even at the level of high amplification and high overexpression, the two do not usually correlate. Polypeptide levels were not investigated. Further, Hyman et al. state that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributed to gene amplification (col. 1, middle, p. 6244). This proportion was about 2% of the total. The Examiner maintains that 2% does not provide a reasonably expectation that the amplification of PRO232 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, the references supports the basis of the rejections that it is more likely than not that gene amplification fails to correlate with increased mRNA/polypeptide levels. Therefore, Hyman et al. also

do not support utility of the claimed polypeptides. Pollack et al. concentrated on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, Platzer et al., who found a poor correlation between DNA amplification and overexpression (p. 12967, col. 2, 7 lines from bottom). Pollack et al. noted that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability, particularly when gene amplification of the instant PRO232 gene has been identified in lung and colon cancer instead of breast tumors.

Appellant argues (paragraph bridging pages 4-5, page 11 and page 20) that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer still has a patentable utility in that it yields more accurate tumor classification and provides significant information for cancer diagnosis and treatment, relying upon the declaration by Dr. Ashkenazi (submitted 12/10/03) and the "real world" example of breast cancer marker HER-2/neu of Hanna et al. reference. Appellant asserts that the Examiner has misread Hanna et al., who state gene amplification and polypeptide expression are well correlated, with only a subset of tumors showing disagreement between the two measurements. Finally, Appellant concludes that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO232 conveys utility to the claimed PRO232 polypeptides. These arguments

have been fully considered but are not found to be persuasive. While it may be true that lack of overexpression of a gene product may also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO232 gene product expression levels to facilitate categorization. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO232 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO232. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. Finally, Hanna et al. supports the rejection in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." This teaches away from using gene amplification in cancer diagnosis or treatment. The identification of

subsets of tumors without correlation affirms the unpredictability of the findings. Therefore, the issues of HER-2 cannot be generalized to any gene expressed in a tumor. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Again, because Hanna et al. studied breast cancer, the warning by Pollack et al. discussed in the preceding paragraph relating to the disparity in correlation of gene amplification and expression in breast compared to colon tumors is significant.

Appellant argues (page 7) "that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use." This statement relates to the Court's decision in *Nelson v. Bowler.* In that decision, the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. However, in this instance, pharmacological activity is not the same as gene amplification. In *Nelson,* the court held that the compound of which utility was in question, was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility. There are no test results to correlate the presence of

PRO232 polypeptide with a diagnostic for lung or colon cancer. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:18 and utility as a cancer diagnostic. A finding of amplification of the genomic nucleic acid of SEQ ID NO:17 cannot be assumed to correlate to the higher expression of the encoded polypeptide in the same tissues.

On page 8, Appellant also cites *Cross v. Iizuka* (Fed. Cir. 1985), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* amplification data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is whether genomic DNA levels correlated with encoded protein levels.

Beginning on the bottom page 10 to page 11, Appellant asserts that patentable utility for the PRO232 polypeptides is based upon the gene amplification data for the gene encoding the PRO232 polypeptide. Appellants concludes that one skilled in the art would consider the 2.056-fold to 5.28-fold amplification of the gene encoding PRO232 in 5 lung tumors and 2.00-fold to 5.32-fold in seven colon tumors is significant and credible. This has been fully considered but is not found to be persuasive. Credibility has never been questioned. However, the significance can be questioned since 14 out of 19 lung tumor and 10/17 colon tumor samples did *not* show an amplification of the gene encoding PRO232, and the control used was not a matched non-tumor lung or colon sample, respectively, but rather was a pooled DNA sample from blood of healthy subjects. As discussed above, the art uses matched tissue

samples. Pennica et al., Konopka et al., Sen et al., Hittelman et al., Godbout et al. and Li et al. speak to the strength of the opposing evidence as discussed in the rejections and response above and no evidence has been provided to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed above. Finally, there is nothing in Example 92 that suggests that the encoded proteins thereof are found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides not genes, the data presented in Example 92 is not sufficient to establish a specific and substantial utility for the encoded and claimed protein.

At page 11 of the Brief, Appellant states that the Examiner asserted that only 5/19 lung tumor and 7/17 colon tumors tested positive for the claimed polypeptide. However, this statement is incorrect, because Example 92 in the instant specification did not measure protein levels, but only genomic DNA levels. Appellant's arguments regarding use of the claimed invention for classification of tumors was addressed early with regard to the Hanna et al. reference.

Appellant argues (beginning at page 12) that Sen et al. supports the position that aneuploidy can be used to diagnose cancerous and precancerous tissue, as well as a means of risk assessment and prognosis. Even if amplification of the PRO232 gene were due to aneuploidy, the art exemplified by Hittelman et al. supports the PRO232 gene as a useful marker for precancerous cells or damaged tissue that could later develop into cancer. Additionally, Hittleman et al. clearly says (p.2, ¶4, line 3), "First, it is important to identify individuals at significantly increased cancer risk who might best

benefit from different types of intervention." The argument has been fully considered, but is not persuasive. In lung, the art shows that both cancerous and noncancerous lung tissue can be aneuploidy (see Sen et al. and Hittelman et al.). Also, in contrast to the art (*e.g.*, see Pennica et al., Konopka et al.), matched tissue samples were not used for controls in determining gene copy number in the instant application. Rather, the control DNA appears to have been isolated from blood. Given these details, one skilled in the art would conclude that data were preliminary. Even though it is desirable to identify individuals at risk for cancer, the claimed invention cannot be used for that purpose. Because it is the PRO232 polypeptide and not the gene which is claimed, even if the reported amplification of the nucleic acid of SEQ ID NO:17 were due to aneuploidy, this does not support a diagnostic utility for the encoded polypeptide or antibody for the reasons previously discussed. The data pertaining to gene amplification do not convey utility to the claimed polypeptides, since amplification in genomic DNA as shown in the art fails to correlate with a corresponding increase in mRNA or polypeptide levels in many cases (see Pennica et al., Konopka et al., Godbout et al. and Li et al.).

Appellant asserts that based on the Ashkenazi Declaration, gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. The Declaration of Dr. Ashkenazi explains that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene

product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product. The Ashkenazi declaration filed under 37 CFR 1.132 (12/10/03) is insufficient to overcome the rejection of the claims based upon lack of utility because: it has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product. Finally, the Ashkenazi declaration supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels.

Appellant asserts that pooled DNA samples from blood of healthy subjects is a proper control for gene amplification assays. Appellant's argument has been fully considered, but is not persuasive. If genomic DNA levels didn't differ from tissue to tissue, then how can a particular DNA be diagnostic for a disease state? Since DNA can be amplified for a number of different reasons (including based on tissue damage from smoking or drinking), then the appropriate control would be the levels of the DNA in normal, healthy tissue rather than blood, absent evidence to the contrary. Additionally, the controls used in Pennica et al. (page 14718, column 1, last full paragraph) were matched tissue samples and Konopka used B-lymphoid cells because this was the sample being tested, contrary to Appellant's assertions. However, even if the prior art uses normal leukocyte DNA as a control in the gene amplification assay, it still does not establish that genomic DNA levels are predictive of protein expression levels and therefore, the data from Example 92 cannot be extrapolated to protein expression levels and the protein still lacks utility.

At page 14 of the Brief, Appellant argues that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels or that polypeptide levels can be "accurately predicted" and that the evidentiary standard to be used is a preponderance of the totality of the evidence under consideration. Appellant then asserts that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellant's argument has been fully considered, but is not found persuasive. Appellant's assessment of the question to be asked is on point and correct. However, a

review of the totality of the evidence under consideration must result in the conclusion that one skilled in the art would reasonably doubt the existence of a positive correlation between protein expression and gene copy number. Appellant again asserts that Orntoft, Hyman and Pollack collectively teach that gene amplification increases mRNA expression. However, the teachings of these references have been addressed and they do not demonstrate that there is a general correlation between gene amplification and mRNA expression, contrary to Appellant's assertion. The instant specification only discloses gene amplification data for PRO232 and does not disclose any information regarding PRO232 mRNA levels and there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues.

At page 15, Appellant characterizes Pennica et al. as being limited to WISP genes and not speaking to the correlation of gene amplification and mRNA or protein expression for genes in general. At page 15-16, Appellant characterizes Konopka et al. as being limited to the *abl* gene, and not speaking to genes in general. Appellant does not need absolute certainty for an asserted use, but only that it is more likely than not that the product has that use. "The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that is it more likely than not, in general, that such a correlation does not exist." This has been fully considered but is not found to be persuasive. Both Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general, because they

show a lack of correlation between gene amplification and gene product overexpression for particular genes. The instant case also concerns a single gene. Pennica et al. showed that 2/3 WISP gene levels did not correlate with mRNA levels. Konopka et al. showed that protein levels for the *abl* gene were due to variation in mRNA levels not gene amplification. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. (see, for example, Godbout et al. and Li et al, discussed below). The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (2) no evidence has been brought forth regarding levels of PRO232 mRNA or polypeptide levels in cancerous tissue. Finally, Pennica et al. provide evidence that closely related WISP genes show unpredictable gene amplification, mRNA and polypeptide levels. As discussed in the rejections above, these references are pertinent to the lack of reasonable expectation that for any given gene the level of gene copy number will correlate with protein expression.

At page 16 of the Brief, Appellant asserts that Orntoft et al., Hyman et al., and Pollack et al. collectively teach that in general, gene amplification increases mRNA expression. Appellant's argument has been fully considered, but is not persuasive. Orntoft et al. used the CGH method to look at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. However, Orntoft et al. do not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time but rather, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See

abstract.). The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO232 in the instant specification. That is, it is not clear whether or not PRO232 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al. does not support utility and enablement of the claimed polypeptides. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO232 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung and colon cancer.

Appellant argues (pages 16-17) that PRO232 was never claimed to be similar to DDX1 of Godbout et al., nor that it was an RNA helicase or confers a selective advantage to cell survival. However, Godbout shows a good correlation between protein levels and genomic DNA amplification. Structure/function data is not a requirement for the utility requirement. The argument has been fully considered, but is not persuasive. Appellant has missed the point of Godbout et al., which is that only those genes which confer a selective advantage to cell survival, for example a RNA helicase (though there are many other types of genes which could confer a selective advantage), would reasonably be expected to be amplified and have a correlative increase in encoded protein. The Examiner cannot find any reason to suspect that the protein encoded by the PRO232 gene would confer any selective advantage on a cell expressing it. On page 21167, right column, first full paragraph, Godbout et al. state, "It is generally accepted that co-amplified genes are not overexpressed unless they provide a selective growth advantage to the cell (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." There is no evidence in the instant application

that PRO232 confers any growth advantage to a cell, and thus it cannot be presumed that the mRNA or protein is overexpressed even if the genomic DNA is amplified. Godbout et al. support the unpredictability that for any particular amplified genomic DNA, the corresponding mRNA or protein will be overexpressed.

Appellant argues (page 17) that Li et al. acknowledge their results differed from those of Hyman et al. and Pollack et al. (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression", with Li et al. noting the difference may be from different methods used to study breast cancer and lung adenocarcinoma. Li et al. used a lower fold amplification threshold (1.40 compared to 2.0 in the instant application). The argument has been fully considered, but is not persuasive. Even if Li et al. used a lower amplification threshold, it was shown that a *significant majority* of genes that are amplified do not have overexpressed mRNA (p. 2633, col. 2, end of first paragraph):

> In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma.

Similarly, Hyman et al. found less than half (44%) of *highly* amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Like Hyman et al., Pollack et al. concentrated on large chromosome regions showing *high* amplification (p. 12965). Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors;

resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability for any particular gene. PRO232 gene has not been asserted to be amplified in breast tumors. Both Li et al. and Hyman et al. show that less than half of the genes showing amplified DNA also showed elevated expression of mRNA. These references in combination with other references such as Godbout et al., Pennica et al. and Konopka et al. support a conclusion that one of skill in the art would not reasonably expect that for any particular amplified gene the corresponding mRNA or protein will more likely than not also be overexpressed.

At page 20 of the Brief, Appellant argues that the Examiner improperly views the further testing described in the Ashkenazi declaration as further characterization of the PRO232 protein itself. Appellant asserts that the experimentation described is only further characterization of the tumor not the polypeptide. Appellant argues that the PRO232 polypeptide is useful in tumor categorization, enabling the physician to select a treatment modality that holds the most promise for successful treatment of a patient. This has been fully considered but is not found to be persuasive. The tissue specific pattern of expression of a protein is definitely a feature of the protein itself. The determination of such is a form of characterizing the protein. Furthermore, no treatment modalities specific to PRO232 have been disclosed in the specification or prior art. The identification of such would require significant further research, thus also indicating that the asserted utility is not substantial.

At page 21 of the Brief, Appellant concludes by arguing that, based on the asserted utility for PRO232 in lung or colon cancer diagnosis, the reduction to practice

of the protein of SEQ ID NO:18, the disclosure of protocols for making chimeric PRO polypeptides such as those claimed and for recombinant expression of PRO232, and the gene amplification assay in Example 92, the skilled artisan would know exactly how to make and use the claimed polypeptide for diagnosis of lung or colon cancers. Appellant urges that testing would have been routine and not undue. This has been fully considered but is not found to be persuasive. The rejection is supported by the preponderance of the evidence. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of noncancerous, damaged lung epithelium (evidenced by Sen et al.). The specification does not assert a utility for PRO232 as a biomarker for damaged, precancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellant (Pennica et al., Godbout et al., Li et al.). Contrary to Appellant's assertions, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Godbout et al., Hyman et al., and Li et al. The declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO232 was tested in normal and cancerous tissue, and

thus the skilled artisan must perform additional experiments, as directed by the art. Since significant further research would have been required of the skilled artisan to reasonably confirm the PRO2932 polypeptide is overexpressed in any cancer to the extent that it could be used as cancer diagnostic agent, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the claimed PRO232 polypeptides could be used as a cancer therapeutic, since there is no evidence that PRO232 plays a role in cancer formation or progression such that inhibiting PRO232 would result in effective cancer therapy. In the absence of information regarding whether or not PRO2932 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO232 polypeptides as diagnostic markers and/or therapeutic target is simply a starting point for further research and investigation into potential practical uses of the claimed polypeptides.

ISSUE 2: Priority of Claims 44-46 and 49-51 based on U.S. Provisional Application 60/059,121, filed September 17, 1997.

Appellant argues that the claimed priority of the instant application is 17 September 1997, and therefore, the rejection is not proper. This argument is not persuasive in light of the utility rejection and the effective priority of the instant application based on the lack of utility.

ISSUE 3: 102(b) rejection of Claims 44-46 and 49-51 by Rosenthal et al. (DE19818619-A1).

Appellant argues that for the reasons discussed above under Issue 2, Rosenthal et al. is not prior art and does not anticipate the claim. Appellant's argument has been fully considered but is not persuasive. Because the instant application fails to provide a specific and substantial utility and also fails to provide an enabling disclosure for the claimed invention, and the prior filed applications also fail to correct this deficiency, the instant application is not entitled to the earlier filing date of the earlier filed applications. Therefore, the filing date for art purposes is the instant filing date, and Rosenthal et al. is prior art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Hearing

It does not appear that Appellants have requested an oral hearing at this time. However, it an oral hearing is requested, the Examiner requests the opportunity to present arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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